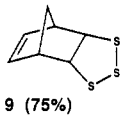
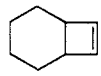
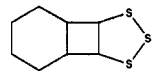
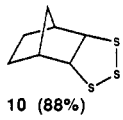
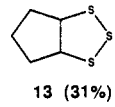
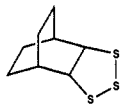
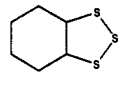
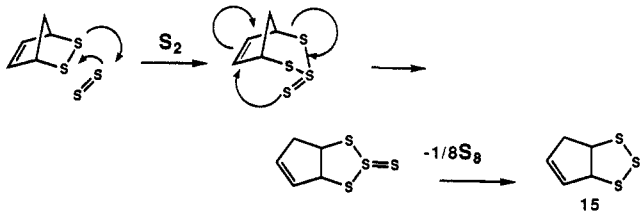
Table I. S_2 Additions to Strained Olefins

Ene	Product (% yield)	Ene	Product (% yield)
	 9 (75%)		 12 (18%)
	 10 (88%)		 13 (31%)
	 11 (15%)		 14 (0%)

Scheme IV

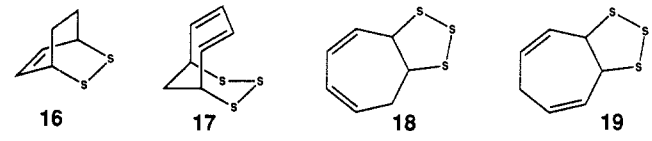


Bicyclic bridged disulfides such as gliotoxin have recently been found to be potent immunomodulating agents.[9] In principle, synthetic entry into this class of compound should be accessible via the addition of S_2 to cyclic 1,3-dienes. We have carried out this type of addition, and the ultimate products obtained, with a single exception, are not the expected bicyclic bridged disulfides but a novel class of allylic epitrisulfide (**5** and **6**, Scheme II) which was difficult to characterize and required us to exclude, by independent syntheses, episulfide formation[10] before we could disclose our findings with some certainty. The allylic epitrisulfide products formed are in striking difference to the products obtained by analogous singlet oxygen chemistry,[11] and we propose an S_2 mechanistic pathway, unavailable to $^1O_2$, to account for it.

Bartlett and Ghosh[12] have reported that norbornadiene reacts with activated elemental sulfur to give [4 + 2] type adduct **7** and its rearranged isomer **8**. We find that S_2 addition, instead, results in the exclusive formation of epitrisulfide **9**[13] (Table I) and that this type of reaction with S_2 appears to be unique to reactive olefins since unstrained olefins, like cyclohexene, are recovered unchanged.

The epitrisulfide products **9-14** (Table I) are formed as a consequence of sulfur deposition from an insertion[15] of a second mole of S_2 to the highly strained S-S bond of the corresponding dithietane precursor intermediates as shown in Scheme III. A similar insertion process followed by a [3,3] sigmatropic rearrangement (Scheme IV) is put forth to account for the allylic epitrisulfide products formed with the cyclic 1,3-dienes.

Although it may be argued that epitrisulfide **15** (Scheme IV) can be derived from cyclopentadiene via a reaction pathway analogous to that for norbornadiene (Scheme III), the [3,3] sigmatropic route is favored from the following two experimental observations. 1,3-Cyclohexadiene reacts with S_2 to give the highly volatile, crystalline Diels-Alder adduct **16** (8% yield) as the sole sulfurated product. Similarly, cycloheptatriene affords only crystalline adduct **17** (20% yield). No trace of the possible dithetane-derived adducts **18** or **19** could be noted.



16 17 18 19

Diels-Alder adduct **16**[13] is the only example of a bicyclic bridged disulfide that we have been able to prepare from S_2 additions.[16] The extreme volatility of this compound, which makes it very difficult to isolate from the reaction medium, is probably also the cause for its being protected from the subsequent and more competitive S_2 insertion into the strained S-S bond. Although the cyclopentadiene adduct should similarly be volatile, the S-S bond in this adduct is much more strained and therefore more susceptible to the S_2 insertion reaction.[15]

Acknowledgment. We thank Professor David N. Harpp for sharing with us unpublished results and for the many stimulating discussions on S_2 chemistry. We are also grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Natural Sciences and Engineering Research Council of Canada as well as the Government of the Province of Quebec for financial support.

Supplementary Material Available: Selected spectral data (^1H NMR, ^{13}C NMR, and HRMS) and selected NMR spectra (6 pages). Ordering information is given on any current masthead page.

(9) Waring, P.; Eichner, R. D.; Mullbacher, A. *Med. Res. Rev.* **1988**, *8*, 499.

(10) Allylic episulfides were synthesized via the methodology of Bombola and Ley (Bombola, M. U.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3013). Spectral data are provided as supplementary material.

(11) Singlet oxygen addition to cyclic 1,3-dienes usually affords the expected bicyclic bridged peroxides. This type of peroxide can be thermally induced to rearrange into its corresponding syn bis(epoxide). See references cited in ref 1a. See also: *Singlet Oxygen Chemistry*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979.

(12) Bartlett, P. D.; Ghosh, T. *J. Org. Chem.* **1987**, *52*, 4937.

(13) All S_2 additions were carried out according to the procedure described in ref 1, and isolated compounds were fully characterized. Spectral data are provided as supplementary material.

(14) Fritz, H.; Weis, C. D. *Tetrahedron Lett.* **1974**, 1659.

(15) Sulfur insertion into strained sulfur-sulfur bonds is well-known. See ref 12, and also see: Murdock, K. C. *J. Med. Chem.* **1974**, *17*, 827. For sulfur deposition, see: Williams, R. C.; Chew, W.; MacDonald, J. G.; Harpp, D. N. *Tetrahedron Lett.*, submitted. Harpp, D. N. *Perspectives in the Organic Chemistry of Sulfur*; Zwanenberg, B., Klunder, A. J. H., Eds.; Elsevier: Amsterdam, 1987.

(16) Harpp and MacDonald[2a] have also prepared this compound using S_2 chemistry.

Ruthenium-Catalyzed Oxidation of Amides and Lactams with Peroxides

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Received February 21, 1990

The oxygenation of C-H bonds adjacent to nitrogen of amides with metal complex catalysts is of importance in view of the xenobiotic metabolism of amino compounds[2] and is one of the most attractive strategies for the synthesis of biologically active nitrogen compounds.[3] Cytochrome P-450 enzymes catalyze specific ox-

(1) (a) Osaka University. (b) Takasago Research Institute Inc.

(2) (a) Gorrod, J. W. *Biological Oxidation of Nitrogen*; Elsevier/North Holland Biomedical Press: New York, 1978. (b) *Cytochrome P-450*; Sato, R., Omura, T., Eds.; Kodansha Ltd: Tokyo, 1978.

(3) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982. (b) Dalton, D. R. *The Alkaloids*; Marcel Dekker: New York, 1979. (c) *Biogenic Amines*; Himwich, H. E., Himwich, W. A., Eds.; Elsevier: Amsterdam, 1964.

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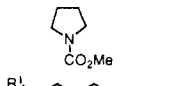
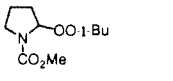
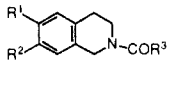
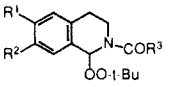
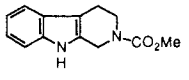
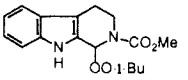
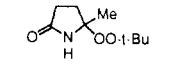
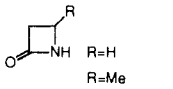
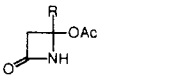
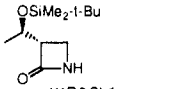
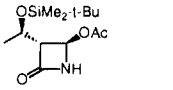
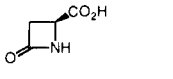
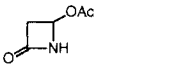
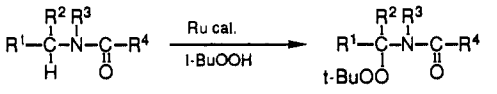
Table I. Ruthenium-Catalyzed Oxidation of Amides and Lactams

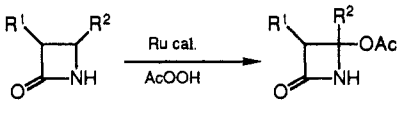
entry	substrate	method[a]	product[b]	yield,[c] %
1		A		60
				
2		A	R^1=H, R^2=H, R^3=OMe	91
3		A	R^1=OCH_2Ph, R^2=OMe, R^3=Me	98
4		A	R^1=OCH_2Ph, R^2=OMe, R^3=OMe	97
5		A		92
6		A		80
7	 R=H	B		94
8	R=Me	B		86
9	 (1′*R*,3*S*)-**1**	B	 (1′*R*,3*R*,4*R*)-**2**	99
10		B		82

[a] The reaction was carried out as described in the text. A: To a mixture of amides and $RuCl_2(PPh_3)_3$ (5 mol %) in benzene was added a *t*-BuOOH solution (3 equiv) in benzene at room temperature. B: AcOOH/Ru-C catalyst. [b] The structure of the product was determined on the basis of the analytical and IR, NMR, and mass spectral data. [c] Isolated yield.

ygenation of amides;[4] however, the biomimetic method for selective oxidation of amides is limited to an electrochemical process.[5] During the course of our study on the simulation of enzymatic function with metal complex catalysts,[6] we have found novel cytochrome P-450 type oxidation of amides and lactams with peroxides. Ruthenium-catalyzed oxidation of amides with *tert*-butyl hydroperoxide under mild conditions gives the corresponding *tert*-butyldioxy amides (eq 1). Similar treatment of β-lactams with peracetic acid in acetic acid gives β-acetoxy β-lactams (eq 2), which are versatile synthetic intermediates for carbapenem antibiotics.[7]



(1)



(2)

The representative results of the oxidation of amides with peroxides are listed in Table I. With *t*-BuOOH as an oxidant (methods A), various *N*-acyl- and *N*-(alkoxycarbonyl)amines can be converted into the corresponding α-(*tert*-butyldioxy)amides highly efficiently. The *tert*-butyldioxy amides of isoquinolines and indoles thus obtained are important synthetic intermediates. The oxidation of γ-substituted γ-lactams gives γ-(*tert*-butyldioxy) lactams (entry 6). The oxidation of ω-unsubstituted lactams such as δ-valerolactam gives the corresponding cyclic imides (62% isolated yield). As a catalyst, $RuCl_2(PPh_3)_3$ has proved to be the most effective for the oxidation of *t*-BuOOH.

Oxidation of β-lactams requires specific reaction conditions because of the higher strain of the four-membered acyliminium ion intermediates. Direct β-acetoxylation of β-lactams can be performed by ruthenium-catalyzed oxidation with peracetic acid in AcOH (method B in Table I). Thus, the ruthenium-catalyzed oxidation of 2-azetidinones with AcOOH in AcOH at room temperature gives 4-acetoxy-2-azetidinones (entries 7 and 8). Importantly, (1′*R*,3*S*)-3-[1′-[(*tert*-butyldimethylsilyl)oxy]-ethyl]azetidin-2-one (**1**)[8] can be converted into (1′*R*,3*R*,4*R*)-4-acetoxy-3-[1′-[(*tert*-butyldimethylsilyl)oxy]ethyl]azetidin-2-one (**2**) with extremely high diastereoselectivity (entry 9). The latter is a versatile and key intermediate for the synthesis of thienamycin and other biologically active β-lactams.[9] β-Carboxy β-lactams undergo decarboxylation and subsequent acetoxylation to give β-acetoxy β-lactams (entry 10). Ruthenium catalysts such as $RuCl_2(PPh_3)_3$, $RuCl_3 \cdot nH_2O$, and Ru on carbon are effective for the oxidation of β-lactams with AcOOH. Although AcOOH is the best oxidant, other oxidants such as *m*-chloroperbenzoic acid, methyl ethyl ketone peroxide, $PhI(OAc)_2$, and PhIO can be used for the acyloxylation of β-lactams. A typical experimental procedure for the oxidation of β-lactams is as follows (method B in Table I). To a mixture of **1** (1.00 g, 4.37 mmol), 5% Ru on carbon (0.25 g), anhydrous AcONa (0.36 g, 4.37 mmol), and AcOH (4.4 mL) was added a 30% solution of AcOOH in AcOEt (2.41 g, 9.61 mmol) dropwise with stirring at room temperature over a period of 2.5 h. After filtration, the mixture was poured into water and extracted with hexane. After the usual workup, evaporation of the solvent gave **2** (1.24 g, 99%) as a colorless solid: mp 108.5 °C; $[\alpha]^{24}_D$ +51.2° (*c* 1.00, $CHCl_3$), lit.[10] $[\alpha]^{25}_D$ +50.0° (*c* 0.41, $CHCl_3$). The diastereomeric excess of **2** was determined to be >99% by means of ^1H NMR and HPLC analyses.

The oxidation can be rationalized as proceeding by a P-450 type mechanism.[6] The ruthenium complex, $RuCl_2(PPh_3)_3$, reacts with *t*-BuOOH to give an oxoruthenium(IV) species,[11] which produces an acyliminium ion intermediate by abstraction of a hydrogen atom from an amide and subsequent electron transfer. Nucleophilic attack of *t*-BuOOH gives the corresponding *tert*-butyldioxygenated product. In the case of the oxidation of β-lactams with AcOOH in AcOH, a similar but more reactive oxoruthenium(IV) species may be formed; nucleophilic attack of AcOH dominates because of its higher nucleophilicity in comparison with AcOOH.[12] Formation of a four-membered acyliminium ion has been confirmed by exclusive formation of the

(4) N-Dealkylation of amides: (a) Low, L. K.; Castagnoli, N., Jr. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1980; Part I, pp 163–167. (b) Shono, T.; Tada, T.; Oshino, N. *J. Am. Chem. Soc.* **1982**, *104*, 2639. (c) Kestell, P.; Threadgill, M. D.; Gescher, A.; Gledhill, A. P.; Shaw, A. J.; Farmer, P. B. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 265.

(5) (a) For an excellent review, see: Shono, T. *Tetrahedron* **1984**, *40*, 811. (b) Acetoxylation of β-lactams: Schneider, P.; Ramos, D.; Bersier, J. EP 290-385-A. (c) Mori, M.; Kagechika, K.; Tohjima, K.; Shibasaki, M. *Tetrahedron Lett.* **1988**, *29*, 1409.

(6) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

(7) For a review, see: Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729.

(8) (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 4961.

(9) (a) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.* **1985**, *26*, 4739. (b) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (c) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *Ibid.* **1986**, *108*, 4675. (d) Meyers, A. I.; Sowin, T. J.; Scholz, S.; Ueda, Y. *Tetrahedron Lett.* **1987**, *28*, 5103. (e) Ito, Y.; Terashima, S. *Ibid.* **1987**, *28*, 6625. (f) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5491. (g) Deziel, R.; Endo, M. *Tetrahedron Lett.* **1988**, *29*, 61. (h) Nagao, Y.; Abe, T.; Shimizu, H.; Kumagai, T.; Inoue, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 821.

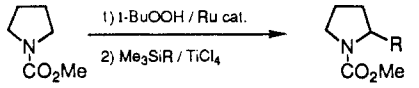
(10) Leanza, W. J.; DiNinno, F.; Muthard, D. A.; Wilkening, R. R.; Wildoger, K. J.; Ratcliff, R. W.; Christensen, B. G. *Tetrahedron* **1983**, *39*, 2505.

(11) (a) For a review, see: Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9. (b) Heimbrook, D. C.; Murray, R. I.; Egeberg, K. D.; Sligar, S. G.; Nee, M. W.; Bruice, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 1514. (c) Burka, L. T.; Guengerich, F. P.; Willard, R. J.; Macdonald, T. L. *Ibid.* **1985**, *107*, 2549.

(12) Bouillon, G.; Lick, C.; Schank, K. In *The Chemistry of Peroxides*; Patai, S., Ed.; John Wiley & Sons: New York, 1983; pp 279–309.

corresponding dichloroacetate upon oxidation of **1** in a mixture of AcOH and Cl_2CHCO_2H (1:1).

The present oxidation reaction provides a novel and convenient method for introduction of substituents at the α-position of amino compounds. Although α-substitution is important in connection with the synthesis of nitrogen-containing biologically active compounds, only a few methods to achieve such substitution are reported.[13] Selective carbon–carbon bond formation at the α-position of amides can be performed readily by alkylation, allylation, and cyanation. Thus, $TiCl_4$-induced reaction of 1-(*tert*-butyldioxy)-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline with benzylmagnesium bromide at −78 °C gave 1-benzyl-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline (71%). Furthermore, 2-(*tert*-butyldioxy)-1-(methoxycarbonyl)pyrrolidine derived from 1-(methoxycarbonyl)pyrrolidine was converted into 2-cyano-1-(methoxycarbonyl)pyrrolidine (**3a**) (77%) or 2-allyl-1-(methoxycarbonyl)pyrrolidine (**3b**) (66%) by $TiCl_4$-induced



3 R = CN
R = $-CH_2CH{=}CH_2$

reactions with cyanotrimethylsilane and allyltrimethylsilane at −78 °C, respectively. Stereoselective carbon–carbon bond formation at the β-position of 4-acetoxyazetidinone **2** has been extensively studied using various nucleophiles.[9]

Work is in progress to provide definitive mechanistic information and to apply the present new method to other systems.

Supplementary Material Available: IR, ^1H NMR, and ^{13}C NMR spectral data for products of ruthenium-catalyzed oxidation of amides and lactams (4 pages). Ordering information is given on any current masthead page.

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Acid-Catalyzed Dehydration of Naphthalene Hydrates

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We wish to report measurements of rates of acid-catalyzed dehydration of the three isomeric hydrates of naphthalene (**1**–**3**). These hydrates have been isolated recently in optically active forms as intermediates in biotransformations of 1,2- and 1,4-dihydronaphthalene by a mutant strain of *Pseudomonas putida*[1,2] and rat liver systems.[3] Preparation of the (racemic) 2-hydroxy-1,2-dihydronaphthalene (**2**) was first reported by Bamberger,[4] and synthetic routes to all three hydrates have since been developed.[5,6]

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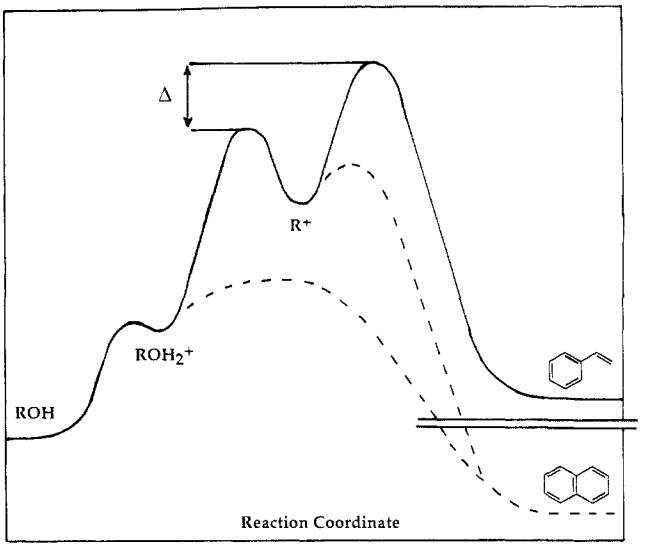
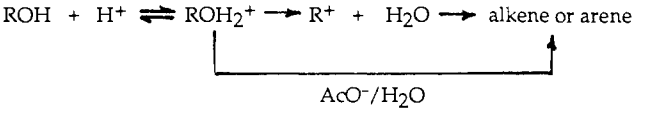
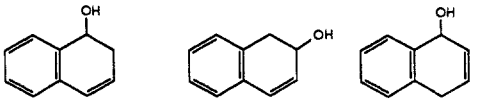


Figure 1.

Scheme I



It was shown by Jeffrey and Jerina that dehydration of **1** and **2** to naphthalene occurs in 1-butanol in the presence of 0.01 M HCl.[6] The reaction also takes place in dilute aqueous solutions of strong acids, and the more reactive 1,4-hydrate **3** dehydrates in acetic acid buffers. Second-order rate constants (M^{-1} s^{-1}) for catalysis by H^+ in aqueous solution, measured spectrophotometrically at 25 °C, are shown under the relevant structures below.



1 0.35 **2** 1.8 **3** 240

Comparisons with simple alcohols show that the hydrates are highly reactive molecules. Thus the saturated acyclic analogue of **1**, α-phenylethanol (**4**), dehydrates nearly 10^8 and 10^{11} times more slowly than the 1,2- and 1,4-hydrates, respectively.[7,8] These differences are too large to be attributed to the activating effect of the vinyl substituent present in the hydrates, and it is natural to ask whether the aromatic stabilization of the naphthalene product is responsible. This stabilization is certainly large. The free energy of hydration of naphthalene may be estimated as ca. 20 kcal/mol,[9] compared with the measured value of −2.2 kcal/mol[7] for styrene, the product of dehydration of α-phenylethanol.

Dehydration of α-phenylethanol occurs in strongly acidic aqueous media, and the mechanism of its reaction is well-established as occurring via the protonated alcohol and the α-phenylethyl carbocation, as shown in the upper pathway of Scheme I.[7] Deprotonation of the carbocation to form styrene is rate-determining, and for the related α-(*p*-methylphenyl)ethanol (**5**) in 1:1 aqueous trifluoroethanol, Jencks and Richard have shown that this occurs nearly 2000 times more slowly than the rate of carbocation formation.[10]

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